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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MODULATION OF IMMUNE SYSTEM FUNCTION BY MODULATION OF POLYPEPTIDE ARGININE METHYLTRANSFERASES

(57) Abstract: The instant invention pertains to, e.g., method of identifying a compound that modulates cytokine production or T cell receptor-mediated signaling, by identifying modulators of the expression and/or activity or PRMT polypeptides. The invention further pertains to methods for identifying a compound that modulates cytokine production in a non-T cell, by identifying compounds that modulate the expression and/or activity of NIP45. Methods for modulating cytokine production in cells by modulating the expression and/or activity of at least one molecule selected from the group consisting of: NIP45, PRMT1, and NFAT are also provided. The invention also pertains to methods for modulating the relative number of Th1 or Th2 cells is modulated and to methods of treating a subject that would benefit from the modulation of cytokine production comprising contacting an immune cell from the subject with an agent that modulates PRMT 1 expression and/or activity in the immune cell.

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/44095

## A. CLASSIFICATION OF SUBJECT MATTER

IPC: C12N 9/10( 2006.01);5/00( 2006.01);A61K 38/16( 2006.01);C07H 21/04( 2006.01)

USPC: 435/193,375;530/358;536/24.5

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
U.S. : 435/193,375; 530/358; 536/24.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
Please See Continuation Sheet

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, T	MOWEN, K. A. et al. Arginine methylation of NIP45 Modulates Cytokine Gene Expression in Effector T Lymphocytes. Molecular Cell. August 2004, Vol. 15, pages 559-571; see the whole article.	1-66
A	PAWLAK, M. R. et al. Arginine N-Methyltransferase 1 Is Required for Early Postimplantation Mouse Development, but Cells Deficient in the Enzyme Are Viable. Molecular and Cellular Biology. July 2000, Vol. 20, pages 4859-4869; see particularly the introduction.	1-66
Y	US 6,090,561 A (GLIMCHER et al.) 18 July 2000 (18.07.2000); see the abstract and claims 8 and 13.	15, 17, 18, 46
A		1-14, 16, 19-47, 49-66

☒ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

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## C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y — A	US 5,858,711 A (GLIMCHER et al. ) 12 January 1999 (12.01.2000); see claim 31.	42, 45, 46 1-41 and 43-44, 47-66
A, P	PAWLAK, M. R. et al Protein Arginine Methyltransferase I: Substrate Specificity and Role in hnRNP Assembly. J. Cell. Biochem. 2002, Vol. 87, pages 394-407, all document.	1-66

## INTERNATIONAL SEARCH REPORT

International application No.

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### Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:  
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

**BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING**

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1, and claims 3, 6-14, all in part, drawn to a method of identifying a compound that modulates cytokine production by selecting a compound that modulates an activity of type I polypeptide arginine methyltransferase (PRMT1).

Group II, claim(s) 2, and claims 3, 6-14, all in part, drawn to a method of identifying a compound that modulates T cell receptor mediated signaling by selecting a compound that modulates an activity of PRMT1.

Group III, claim(s) 4 and 5, drawn to a method of identifying a compound that modulates cytokine production by selecting a compound that modulates expression of PRMT1.

Group IV, claim(s) 15-19, drawn to a method of identifying a compound that modulates cytokine production in non-T cell by selecting a compound that modulates activity of NIP45 which is binding to NFAT or PRMT1.

Group V, claim(s) 20-32, drawn to a method of identifying a compound that modulates cytokine production in non-T cell by selecting a compound that modulates activation of IL-4, IFN- $\gamma$ , Erg2, Erg3, c-Rel and p65 genes.

Group VI, claims 33-41, drawn to a method for identifying a compound that modulates an interaction between NIP45 and PRMT polypeptide.

Group VII, claims 42-47, drawn to a method for identifying a compound that modulates cytokine production in a cell using a nucleotide sequence encoding at least one activator of cytokine gene transcription, e.g. NFATc2, NIP45 and c-maf.

Group VIII, claims 48-49 and claims 55-56 in part, drawn to a method for modulating cytokine production in a non-T cell using an agent that modulates expression and/or activity of NIP45, PRMT1 or NFAT.

Group IX, claims 50-54 and claims 55-56 in part, drawn to a method for modulating cytokine production in T cells by an agent that modulates PRMT1 expression or activity.

Group X, claims 57-58 directed to a method for modulating IFN $\gamma$  production by an agent that modulates PRMT1 expression.

Group XI, claims 59-60, directed to a method for modulating IL4 production by an agent that modulates PRMT1 expression or activity.

Group XII, claims 61, 63 and 65 directed to a method for modulating the relative number of Th1 or Th2 cells by an agent that modulates PRMT1 activity.

Group XIII, claims 62, 64 and 66 directed to a method of treating a subject by an agent that modulates PRMT1 expression and/or activity, to modulate in said subject cytokine production.

The inventions listed as Groups I-XIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: they are directed to methods of identifying and/or using the following

- 1) an agent that modulates activity of PRMT1,
- 2) a compound that modulates expression of PRMT1,
- 3) a compound that modulates binding of NIP45 to NFAT,
- 4) a compound that modulates binding of NIP45 to PRMT1,
- 5) a compound that modulates activation of IL-4,
- 6) a compound that modulates activation IFN $\gamma$ ,
- 7) a compound that modulates activation Erg2,

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- 8) a compound that modulates activation Erg3,
- 9) a compound that modulates activation of c-Rel,
- 10) a compound that modulates activation of p65,
- 11) a DNA molecule encoding NFKB2,
- 12) a DNA molecule encoding NIP45, and
- 13) a Dna molecule encoding c-maf.

Thus, the claims possess many special technical features, i.e., they do not possess one special technical feature.

## Continuation of B. FIELDS SEARCHED Item 3:

Medline, WEST

PRMT1 and NIP45, inventors' patents